ANALYSIS OF A MATHEMATICAL MODEL OF RHEUMATOID ARTHRITIS

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Abstract. Rheumatoid arthritis is an autoimmune disease characterized by inflammation in the synovial fluid within the synovial joint connecting two contiguous bony surfaces. The inflammation diffuses into the cartilage adjacent to each of the bony surfaces, resulting in their gradual destruction. The interface between the cartilage and the synovial fluid is an evolving free boundary. In this paper we consider a two-phase free boundary problem based on a simplified model of rheumatoid arthritis. We prove global existence and uniqueness of a solution, and derive properties of the free boundary. In particular it is proved that the free boundary increases in time, and the cartilage shrinks to zero as $t \to \infty$, even under treatment by a drug. It is also shown in the reduced one-phased problem, with cartilage alone, that a larger prescribed inflammation function leads to a faster destruction of the cartilage.

1. Introduction

Free boundary problems arise in many models of biological processes. These include the healing/closure of a wound [1, 2], growth of a plaque in the artery [3, 4], aortic aneurysm [5], formation of granulomas [6, 7], biofilms [8, 9], platelet deposition [10], and cancer; cancer has been the most active area, so we just refer to recent articles on cancer and cancer therapy [11, 12, 13]. Some of the models have been studied by rigorous mathematical analysis: wound healing [14, 15], biofilms [16], platelet deposition [17], granulomas [18, 19], stability of steady plaques [20]. A review of mathematical analysis of cancer models appears in [21]. There are also analytical results on free boundary problems modeling infectious diseases, ecological interactions [22, 23, 24, 25], and physical processes such as grain hydration [26].

More recently, a mathematical model of rheumatoid arthritis, an autoimmune disease, was developed in [27]. The hallmark of the disease is the progressive destruction of the cartilage in the synovial joint. The boundary of the cartilage, which is in contact with the synovial fluid, is a free boundary. In the present paper we study, by rigorous mathematical analysis, a simplified model that includes much of the biology of the complete model in [27], and prove various properties of the free boundary.

A synovial joint is a freely movable joint in which contiguous bony surfaces are covered by articular cartilages and connected by fibrous connective tissue capsule lined with synovial membrane. The cavity bounded by the synovial membranes is filled with synovial fluid which is secreted by cells that reside in the synovial membrane. The cartilage reduces the friction and the synovial fluid acts as shock absorber during movement of the contiguous bones.

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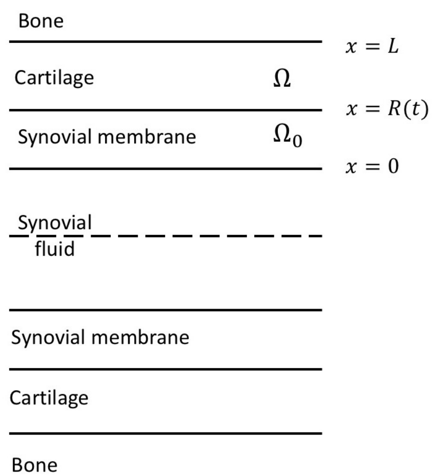
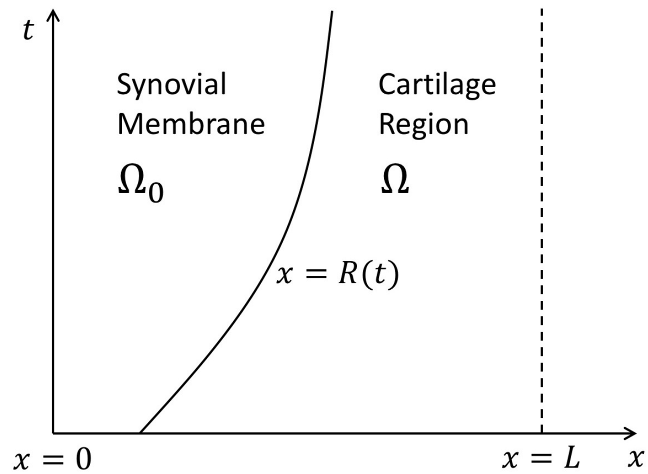
Rheumatoid arthritis (RA) is an autoimmune disease that affects the synovial joints. It is characterized by synovial inflammation which may result in cartilage and bone destruction. The inflammation orginates in the synovial membrane when inflammatory cytokines are being produced by pro-inflammatory cells. The cytokines diffuse into the cartilage, and cause its gradual degradation. Figure 1(a) shows a simplified geometry of a synovial joint.



(A)



(B)

FIGURE 1. (A) The simplified geometry of a synovial joint; (B) The graph of free boundary $x = R(t)$ separating the synovial membrane and the cartilage region.

A mathematical model of RA, based on the geometry of Figure 1 was recently developed by N. Moise and A. Friedman [27]. Simulations of the model show that the interface between the cartilage and the synovial membrane, $x = R(t)$, is continuously increasing with t, as in Figure 1(b), and its growth can be slowed, but not stopped, by various drugs. The model consists of a system of partial differential equations for cells and the cytokines which they produce, with $x = R(t)$ as a free boundary. The cells are macrophages, T cells and fibroblasts in the synovial membrane, and chondrocytes (C) in the cartilage. The cartilage consists mostly of the extracellular matrix (ECM) with density ρ, made up by collagens, and the collagens are produced by the chondrocytes. The inflammation (μ) is produced in the synovial membrane and it spreads into the cartilage, where it accelerates the death of chondrocytes and, thereby, the destruction of the ECM.

The aim of the present paper is to derive, by rigorous analysis, various properties of the free boundary for a simplied version of the full model of [27].

In Section 2 - 5 we consider a model in the cartilage region only, with the level of inflammation $\mu(x, t)$ being a given function. In Section 2 we introduce the mathematical model, and in Section 3 we prove existence and uniqueness of the solution. In Section 4 we establish a comparison theorem, namely: If $\mu_1(x,t) > \mu_2(x,t)$ for all (x,t), then the corresponding free boundaries $x = R_{\mu_1}(t)$ and $x = R_{\mu_2}(t)$ satisfy the inequality

$$R_{\mu_1}(t) > R_{\mu_2}(t) \quad \text{for all } t > 0,$$

that is, a higher level of inflammation results in a faster degradation of the cartilage.

In Section 5 we consider the asymptotic behavior of $R(t)$. We address the question whether the cartilage will be completely destroyed as $t \to \infty$, that is, $\lim_{t\to\infty} R(t) = L$, or whether a part of the cartilage will remain intact for all time, that is, $\lim_{t\to\infty} R(t) < L$. Answers are given under several sharp conditions on $\mu(x,t)$.

In Sections 6 - 9 we consider an RA model with both the synovial membrane and cartilage regions. The model, introduced in Section 6, is a simplified version of the RA model of [27]. In Section 7 we prove existence and uniqueness of the solution. In Section 8 we extend the results of Section 4 to the two-phase problem, showing that the inflammation is a monotone decreasing function of x. This is used in Section 9 to prove that giving a drug can delay the destruction of the cartilage; however, the cartilage always disappear as $t \to \infty$.

2. The one-phase mathematical model

We denote by Ω the cartilage region,

$$\Omega = \{(x,t) : R(t) \le x \le L,\, t > 0\},$$

and by Γ its free boundary

$$\Gamma = \{(R(t),t) :\, t > 0\}.$$

We introduce two variables: $C =$chondrocytes density, and $\rho =$ ECM density, and assume that

$$C + \rho = \text{ const. } = \theta \quad \text{in } \Omega, \tag{2.1}$$

where the constant θ depends on the parameters of the model, except μ. These functions satisfy the following conservation laws in Ω:

$$\frac{\partial C}{\partial t} + \frac{\partial}{\partial x}(uC) = A_C - d_C C - \mu(x,t)C, \tag{2.2}$$

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(u\rho) = \lambda_{\rho C} C - d_\rho \rho, \tag{2.3}$$

where $u = u(x,t)$ is the advection velocity, $\mu(x,t) \ge 0$, the constant A_C is a source and d_C is the death rate of chondrocytes, $\lambda_{\rho C}$ is the production rate of the ECM by chondrocytes, and d_ρ is the depletion rate of the ECM. Inflammation increases the death of chondrocytes at rate $\mu(x,t)$; for simplicity we refer to $\mu(x,t)$ as the inflammation. Using the assumption (2.1) we can derive an equation for u by adding equations (2.2)-(2.3),

$$\theta\frac{\partial u}{\partial x} = (A_C - d_\rho\theta) + \beta C - \mu C,$$

where

$$\beta = -d_C + \lambda_{\rho C} + d_\rho.$$

In healthy steady state without inflammation (i.e. $\mu = 0$), we have $C \equiv C_0$ and $\rho \equiv \rho_0$, and

$$C_0 + \rho_0 = \theta, \quad A_C - d_C C_0 = 0, \quad \lambda_{\rho C} C_0 - d_\rho \rho_0 = 0.$$

Hence

$$\frac{d_\rho\theta - A_C}{C_0} = \frac{d_\rho(C_0+\rho_0) - d_C C_0}{C_0} = d_\rho + \lambda_{\rho C} - d_C = \beta$$

so that

$$-\frac{\partial u}{\partial x} = \frac{1}{\theta}\left[\beta(C_0 - C) + \mu C\right]. \tag{2.4}$$

We assume that $\beta > 0$; in [27] $\beta \approx 5.25$.

We next assume that the velocity is zero at the cartilage-bone interface, $x = L$:

$$u(L,t) = 0 \quad \text{for} \ \ t > 0. \tag{2.5}$$

Hence we can integrate (2.4) to obtain

$$u(x,t) = \frac{1}{\theta}\int_x^L \left[\beta(C_0 - C(x,t)) + \mu(x,t)C(x,t)\right] dx. \tag{2.6}$$

We also assume that the free boundary moves with the velocity u of chondrocytes and ECM at the membrane-cartilage interface, $x = R(t)$:

$$\frac{dR}{dt}(t) = u(R(t),t) = \frac{1}{\theta}\int_{R(t)}^L \left[\beta(C_0 - C(x,t)) + \mu(x,t)C(x,t)\right] dx. \tag{2.7}$$

We prescribe initial data $R_{\rm in}$ and $C_{\rm in}(x) = C(x,0)$:

$$0 < R_{\rm in} < L, \quad \text{and} \quad 0 < C_{\rm in}(x) \le C_0 \quad \text{for} \ \ R_{\rm in} \le x \le L, \tag{2.8}$$

and assume that

$$\|\mu\| = \sup_{\substack{0 \le x \le L,\\ t \ge 0}} \mu(x,t) < \infty. \tag{2.9}$$

The system of equations (2.2), (2.6), (2.7) with the conditions (2.5), (2.8), (2.9) is a free boundary problem for C with non-local coefficients given by the velocity u. It will be convenient to rewrite (2.2) in the form

$$\frac{\partial C}{\partial t} + u\frac{\partial C}{\partial x} = d_C(C_0 - C) - \mu C - C\frac{\partial u}{\partial x},$$

and, by substituting $\frac{\partial u}{\partial x}$ from (2.4), we obtain:

$$\frac{\partial C}{\partial t} + u\frac{\partial C}{\partial x} = g(C) - \mu C\left(1 - \frac{C}{\theta}\right) \tag{2.10}$$

where

$$g(C) = \left(d_C + \frac{\beta}{\theta}C\right)(C_0 - C). \tag{2.11}$$

Note that $1 - \frac{C}{\theta} > 0$ since $C + \rho = \theta$ and $\rho > 0$ (since initially $\rho = \theta - C \geq \theta - C_0 = \rho_0 > 0$).

Biological consideration implies that the following inequality must hold:

$$\mu(x, t) \leq \beta. \tag{2.12}$$

Indeed, consider, at some initial time $t = t_0$, two models with the same $R(t_0)$ and $\mu(x, t)$, but with

$$C_1(x, t_0) < C_2(x, t_0) \quad (R(t_0) \leq x \leq L).$$

We expect that for the model with C_1 the cartilage thickness $L - R_1(t)$ will begin to decrease at a higher rate than that of the cartilage thickness $L - R_2(t)$ for the model with C_2. Hence, by (2.7),

$$0 \leq \frac{d(R_1 - R_2)}{dt}\bigg|_{t=t_0} = \int_{R(t_0)}^{L} [\beta - \mu(x, t_0)][C_2(x, t_0) - C_1(x, t_0)]\, dx.$$

Since this inequality should be valid for arbitrary $C_2(x, t_0) - C_1(x, t_0) \geq 0$, it implies that (2.12) holds.

We finally mention that it is natural to assume that

$$\frac{\partial \mu}{\partial x}(x, t) \leq 0, \tag{2.13}$$

since the inflammation originates in the region $\{0 < x < R(t)\}$ and it decreases as it diffuses deeper into the cartilage [27].

In Section 3, we prove existence and uniqueness of the solution (C, u, R) for all $t > 0$, with continuous $\frac{dR}{dt}$.

In Sections 4 and 5 we shall assume conditions (2.12) and (2.13) and establish properties of the free boundary Γ.

3. Existence and uniqueness of the one-phase problem

In this section we prove the existence and uniqueness of a solution of the free boundary problem (2.2), (2.5)-(2.8) for all $t \geq 0$. We begin with the following a priori estimate:

Lemma 3.1. *Suppose* $0 < C_{\rm in}(x) \leq C_0$*, then*

$$\min\left\{\inf_{R_{\rm in}<x<L} C_{\rm in}, C_*\right\} \leq C(x,t) \leq C_0 \quad \textit{for} \;\; R(t) < x < L,\, t > 0.$$

where

$$C_* = C_*(\|\mu\|) = \inf\left\{s \in (0, C_0) : g(s) - \|\mu\| \left(1 - \frac{s}{\theta}\right) s = 0\right\} \in (0, C_0).$$

Proof. The quadratic polynomial $G(s) := g(s) - \|\mu\| \left(1 - \frac{s}{\theta}\right) s$ satisfies

$$G(0) = d_C C_0 > 0 \quad \text{and} \quad G(C_0) = -\|\mu\| \left(1 - \frac{C_0}{\theta}\right) C_0 < 0.$$

Hence it has a unique zero C_* in the interval $(0, C_0)$ and $G(s) > 0$ if $0 \leq s < C_*$, $G(s) < 0$ if $C_* < s < C_0$. Next, fix $t_0 > 0$ and $x_0 \in (R(t_0), L)$, and let $X(t)$ be the characteristic such that $X'(t) = u(X(t), t)$ and $X(t_0) = x_0$. Then, by (2.10), the function $\Phi(t) := C(X(t), t)$ satisfies:

$$\frac{d\Phi}{dt}(t) = \frac{\partial C}{\partial t} + u\frac{\partial C}{\partial x} = g(\Phi(t)) - \mu(X(t), t) \left(1 - \frac{\Phi(t)}{\theta}\right) \Phi(t).$$

Since $\Phi(0) \leq C_0$ and the right-hand side is negative in case $\Phi(t) = C_0$, we deduce that $\Phi(t) \leq C_0$ for all $t \geq 0$. Hence $C(x_0, t_0) \leq C_0$. Similarly, we may rewrite

$$\frac{d\Phi}{dt}(t) = \frac{\partial C}{\partial t} + u\frac{\partial C}{\partial x} \geq G(\Phi(t)),$$

and hence $\Phi(t) \geq \min\{\Phi(0), C_*\}$, and, in particular, $C(x_0, t_0) \geq \min\left\{\inf_{R_{\rm in}<x<L} C_{\rm in}, C_*\right\}$. $\square$

Corollary 3.2. *From* (2.6), (2.7) *and the inequality* $C(x,t) \leq C_0$*, it follows that*

$$u(x,t) \geq 0 \quad \textit{for } R(t) \leq x \leq L,\, t > 0, \tag{3.1}$$

$$\frac{dR(t)}{dt} \geq 0 \quad \textit{for } t > 0, \tag{3.2}$$

and the inequalities are strict if $\mu(x,t) > 0$ *for all* (x,t)*.*

Theorem 3.3. *Let* $R_{\rm in} \in (0, L)$ *and* $C_{\rm in}(x) \in C^1([R_{\rm in}, L]; [0, C_0])$ *be fixed and* $\mu \in C([R_{\rm in}, L]\times [0,\infty))$ *be uniformly bounded (as in* (2.9)*), then the system of equations* (2.2), (2.6), (2.7), *with the conditions* (2.5) *and* (2.8), *has a unique solution*

$$(C(x,t), u(x,t), R(t)) \in C^1(\bar\Omega) \times C^1(\bar\Omega) \times C^1([0,\infty)),$$

where $\Omega = \{(x,t):\ t>0,\ R(t) \le x \le L\}$. *Moreover,* $R(t) < L$ *for all* $t \ge 0$.

Proof. We note that, for local-in-time existence, one can argue as in [28, Theorem 2.3]. We give a direct proof here based on elementary arguments. We first transform the problem to a fixed domain $[R_{\rm in}, L] \times [0, T]$. For a given solution $(C(x,t), u(x,t), R(t))$ (defined in $\{(x,t) : 0 \le t \le T,\ R(t) \le x \le L\}$), we let $X(x,t) \in C^1([0,T] \times [R_{\rm in}, L])$ be the corresponding characteristic curves so that

$$\frac{\partial}{\partial t} X(x,t) = u(X(x,t), t), \quad \text{and} \quad X(x,0) = x \quad \text{for } R_{\rm in} \le x \le L, \tag{3.3}$$

and we set $\hat C(x,t) := C(X(x,t), t)$.

Claim 1. $(C(x,t), u(x,t), R(t))$ *is a solution to the free-boundary problem if and only if* $(\hat C(x,t), X(x,t)) \in C^1([0,T]; C([R_{\rm in}, L]) \times C^1([R_{\rm in}, L]))$ *satisfies the system*

$$\begin{cases} \frac{\partial}{\partial t}\hat C(x,t) = \hat G(t, \hat C(x,t), X(x,t)) & \text{for } t \in [0,T] \text{ and } x \in [R_{\rm in}, L], \\ \frac{\partial}{\partial t} X(x,t) = \int_x^L \frac{\partial X}{\partial y}(y,t) \hat H(t, \hat C(y,t), X(y,t))\,dy & \text{for } t \in [0,T] \text{ and } x \in [R_{\rm in}, L], \\ \hat C(x,0) = C_{\rm in}(x) & \text{for } x \in [R_{\rm in}, L], \\ X(x,0) = x & \text{for } x \in [R_{\rm in}, L], \end{cases} \tag{3.4}$$

where

$$\begin{cases} \hat G(t,p,q) = \left(d_C + \frac{\beta}{\theta} p\right)(C_0 - p) - \mu(q,t) p \left(1 - \frac{p}{\theta}\right), \\ \hat H(t,p,q) = \frac{1}{\theta}\left[\beta(C_0 - p) + \mu(q,t) p\right]. \end{cases} \tag{3.5}$$

It is straightforward to see that if $(C(x,t), u(x,t), R(t))$ is a solution to (2.2), (2.6), (2.7), with the conditions (2.5) and (2.8), then $(\hat C(x,t), X(x,t))$ is a solution to (3.4).

Conversely, if $(\hat C(x,t), X(x,t))$ is a solution to (3.4), then we need to show the following:

Claim 2. $\frac{\partial X}{\partial x}(x,t) > 0$ *for all* (x,t). *In particular,* $x \mapsto X(x,t)$ *is invertible for each* t.

To this end, observe that $\frac{\partial X}{\partial x}(x,0) = 1 > 0$ and

$$\frac{\partial}{\partial t}\left(\frac{\partial X}{\partial x}\right) = -\hat H(t, \hat C(x,t), X(x,t)) \frac{\partial X}{\partial x}, \tag{3.6}$$

and hence $\frac{\partial X}{\partial x} > 0$ for all x and t. This shows that the inverse function $X^{-1}(\cdot,t) : [X(R_{\text{in}},t),L] \to [R_{\text{in}},L]$ such that

$$x = X^{-1}(y,t) \quad \Longleftrightarrow \quad y = X(x,t)$$

is well-defined. Finally, it is straightforward to verify that the functions

$$\begin{cases} C(x,t) := \hat{C}(X^{-1}(x,t),t) \\ u(x,t) := \int_{X^{-1}(x,t)}^{L} \frac{\partial X}{\partial y}(y,t)\hat{H}(t, C(X(y,t),t), X(y,t))\,dy \\ R(t) := X(R_{\text{in}},t). \end{cases} \tag{3.7}$$

solves (2.2), (2.6), (2.7), with the conditions (2.5) and (2.8). This establishes the claim.

Next, observe that the system (3.4) defines an initial value problem of $(\hat{C},X)$ in the Banach space $C^1([R_{\text{in}},L]) \times C^1([R_{\text{in}},L])$, from which local existence and uniqueness follows.

For global existence, we note that as long as the solution exists,

$$\|\hat{C}(\cdot,t)\|_{C([R_{\text{in}},L]))} \le C_0, \quad \|X(\cdot,t)\|_{C([R_{\text{in}},L]))} \le L \quad \text{and} \quad R(t) = X(R_{\text{in}},t) < L. \tag{3.8}$$

Indeed, the first inequality is a consequence of Lemma 3.1. For the other two estimates, observe that $\frac{\partial X}{\partial x} > 0$ for all x,t (by Claim 2) and that $X(L,t) \equiv X(L,0) = L$ for all $t > 0$, by substituting $x = L$ in the second equation of (3.4). Hence we have $0 \le X(x,t) < X(L,t) = L$ for all $x \in [0,L)$ and $t > 0$. Finally, recall that $R(t) = X(R_{\text{in}},t)$, so that $R(t) < L$ holds as well. Using (3.8) we can deduce from (3.4) (as in [28, Lemma 2.2]) that, for any $T > 0$,

$$\begin{aligned} &\sup_{0\le t\le T} (\|\hat{C}(\cdot,t)\|_{C^1([R_{\text{in}},L])} + \|X(\cdot,t)\|_{C^1([R_{\text{in}},L])}) \\ &\le M_1 T \int_0^T (\|\hat{C}(\cdot,t)\|_{C^1([R_{\text{in}},L])} + \|X(\cdot,t)\|_{C^1([R_{\text{in}},L])})\,dt \end{aligned} \tag{3.9}$$

where the constant M_1 depends on the bounds of $\hat{G}$ and $\hat{H}$ and the partial derivatives in p,q up to first order, in the set $(t,p,q) \in \mathbb{R}_+ \times [0,C_0] \times [0,L]$ and this constant M_1 is independent of T. This proves that $\|\hat{C}(\cdot,t)\|_{C^1([R_{\text{in}},L])} + \|X(\cdot,t)\|_{C^1([R_{\text{in}},L])}$ does not blow-up. Thus the solution can be extended step-by-step to all of $t \ge 0$. This proves the global existence of a solution $(\hat{C},X) \in C^1([0,\infty); C^1([R_{\text{in}},L]) \times C^1([R_{\text{in}},L]))$ to (3.4), and recalling (3.7), the proof of the theorem is complete. □

Remark 3.4. (a) *If $\mu \in C^1([R_{\text{in}},L] \times [0,T])$ and $C_{\text{in}} \in C^2([R_{\text{in}},L])$, then the system* (3.4) *then defines an initial value problem for $(\hat{C},X)$ in $C^2([R_{\text{in}},L])$. Hence, the solution (C,u,R) satisfies the additional regularity:*

$$(C_x,u_x) \in C^1(\bar{\Omega};\mathbb{R}^2), \quad \text{and} \quad R \in C^2([0,\infty)),$$

where we used also (2.7).

(b) *Let* (R_i, C_i, u_i) $(i = 1, 2)$ *be the unique solutions to the system of equations* (2.2), (2.6), (2.7), *with the conditions* (2.5), *that corresponds to the same initial conditions* (2.8) *but to different inflammation functions* $\mu_1, \mu_2 \in C([R_{\text{in}}, L] \times [0, T])$.

By the system (3.4), *we observe that*

(3.10)
$$\sup_{[0,T]} \left[\|\hat{C}_1(\cdot,t) - \hat{C}_2(\cdot,t)\|_{C([R_{\text{in}},L])} + \|X_1(\cdot,t) - X_2(\cdot,t)\|_{C([R_{\text{in}},L])} + |R_1(t) - R_2(t)|\right] \leq M_0 T \|\mu_1 - \mu_2\|_{C([R_{\text{in}},L]\times[0,T])}$$

where $X_i(x,t)$ *is the characteristic curves corresponding to* u_i *given by* (3.3) *and* $\hat{C}_i(x,t) = C(X_i(x,t),t)$.

4. Comparison theorems

Lemma 4.1. *If* $\mu \in C^1([R_{\text{in}}, L] \times [0, \infty))$ *and* $C_{\text{in}} \in C^2([R_{\text{in}}, L])$, *and*

$$\frac{\partial \mu}{\partial x}(x,t) < 0 \quad \textit{for } \ 0 < x < L,\ t \geq 0, \qquad \textit{and} \qquad \frac{\partial C_{\text{in}}}{\partial x} > 0 \quad \textit{for } \ R_{\text{in}} \leq x \leq L,$$

then

$$\frac{\partial C}{\partial x}(x,t) > 0 \quad \textit{for } \ R(t) \leq x \leq L,\ t > 0.$$

Proof. Set $C_x = \frac{\partial C}{\partial x}$ and $\mu_x = \frac{\partial \mu}{\partial x}$. Initially $C_x(x,0) \geq 0$ for all x. We claim that along each characteristic path $X(t)$, $C_x(X(t),t) > 0$ for $t > 0$. Indeed, by Remark 3.4(a), we may differentiate (2.10) to obtain

$$\frac{\partial C_x}{\partial t} + u\frac{\partial C_x}{\partial x} = g'(C)C_x - \mu\left(1 - \frac{2C}{\theta}\right)C_x - \frac{\partial u}{\partial x}C_x - \mu_x C\left(1 - \frac{C}{\theta}\right), \tag{4.1}$$

or, along characteristics,

$$\frac{DC_x}{Dt} := \frac{\partial C_x}{\partial t} + u\frac{\partial C_x}{\partial x} = F(C,\mu)C_x + b(x,t),$$

where $b = -\mu_x C\left(1 - \frac{C}{\theta}\right) > 0$. Since $C_x > 0$ at $t = 0$, it follows that C_x remains positive for all $t > 0$. □

Fix initial data $(R_{\text{in}}, C_0(x))$ and consider two different inflammation functions, μ_1 and μ_2. We denote by (C_i, u_i, R_i) the solution corresponding to μ_i.

Theorem 4.2. *Assume that*

$$\mu_1(x,t) > \mu_2(x,t) \quad \textit{for all } \ 0 \leq x < L,\ 0 < t \leq T, \tag{4.2}$$

$$\frac{\partial \mu_1}{\partial x}(x,t) < 0 \quad \textit{for all } \ 0 \leq x < L,\ 0 < t \leq T, \tag{4.3}$$

and

$$\mu_2(x,t) \leq \beta \quad \text{for all } \ 0 \leq x \leq L,\ 0 < t \leq T, \tag{4.4}$$

Then

$$R_1(t) > R_2(t) \quad \text{for all } \ 0 < t \leq T, \tag{4.5}$$

$$C_1(x,t) < C_2(x,t), \quad \text{for all } \ R_1(t) \leq x \leq L,\ 0 < t \leq T, \tag{4.6}$$

and

$$u_1(x,t) > u_2(x,t) \quad \text{for all } \ R_1(t) \leq x < L,\ 0 < t \leq T. \tag{4.7}$$

Proof. Define the interval

$$I = \{t' \geq 0 : \ (4.5) \ \text{and} \ (4.6) \ \text{holds for all } t \in (0,t'].\}$$

First we show $I \neq \emptyset$. Since $R_1(0) = R_2(0) = R_{\text{in}}$, and

$$\begin{aligned} \frac{d(R_1 - R_2)}{dt}\Big|_{t=0} &= \int_{R_{\text{in}}}^{L} \left[(\beta - \mu_2)(C_2 - C_1) + (\mu_1 - \mu_2)C_1\right] \, dx\Big|_{t=0} \\ &= \int_{R_{\text{in}}}^{L} (\mu_1(x,0) - \mu_2(x,0)) C_{\text{in}}(x) \, dx > 0, \end{aligned}$$

the inequality (4.5) holds for $0 < t \ll 1$.

Next, define $\tilde{C}(x,t) := C_1(x,t) - C_2(x,t)$. Since $C_1(x,0) = C_2(x,0) = C_{\text{in}}(x)$, it follows that $\tilde{C}(x,0) = \frac{\partial \tilde{C}}{\partial x}(x,0) = 0$. It follows then from (2.10) that, along characteristics,

$$\frac{\partial \tilde{C}}{\partial t}(x,0) = (\mu_2 - \mu_1) C_{\text{in}} \left(1 - \frac{C_{\text{in}}}{\theta}\right) < 0 \quad \text{for } \ R_{\text{in}} \leq x \leq L.$$

Therefore $\sup_x \tilde{C}(x,t) < 0$ for $0 < t \ll 1$, i.e. (4.6) holds for $0 < t \ll 1$. This proves $I \neq \emptyset$.

Since I is an open set, we deduce that $I = [0,t^*)$, for some $t^* \in (0,T]$. We claim that (4.7) holds for $t \in (0,t^*)$. Indeed, this follows from (2.6):

$$\begin{aligned} u_1(x,t) - u_2(x,t) &= \tfrac{1}{\theta} \textstyle\int_x^L [(\beta - \mu_2)(C_2 - C_1) + (\mu_1 - \mu_2)C_1] \, dx \\ &\geq \tfrac{1}{\theta} \textstyle\int_x^L (\mu_1 - \mu_2) C_1 \, dx > 0. \end{aligned} \tag{4.8}$$

It remains to show that I is closed in $(0,T]$. Assume, for contradiction, that $I = (0,t^*)$. Then by continuity,

$$R_1(t) \geq R_2(t), \quad C_1(x,t) \leq C_2(x,t), \quad u_1(x,t) \geq u_2(x,t), \tag{4.9}$$

for $R_1(t) \le x \le L$, and $t \in (0, t^*]$. Now, by (2.7),

$$\begin{aligned}
\frac{d}{dt}(R_1(t) - R_2(t)) &= \int_{R_1(t)}^{L} [\beta(C_0 - C_1) + \mu_1 C_1]\, dx - \int_{R_2(t)}^{L} [\beta(C_0 - C_2) + \mu_2 C_2]\, dx \\
&= \int_{R_1(t)}^{L} [(\beta - \mu_2)(C_2 - C_1) + (\mu_1 - \mu_2)C_1]\ dx - \int_{R_2(t)}^{R_1(t)} [\beta(C_0 - C_2) + \mu_2 C_2]\, dx \\
&\ge \int_{R_1(t)}^{L} (\mu_1 - \mu_2) C_1(x,t)\, dx - (\beta + \|\mu_2\|) C_0 (R_1(t) - R_2(t))
\end{aligned}$$

for $t \in (0, t^*]$. Since $R_1(0) = R_2(0) = R_{\text{in}}$, we can integrate the above to obtain

$$R_1(t) - R_2(t) \ge \int_0^t e^{-(\beta + \|\mu_2\|)C_0(t - t')} \int_{R_1(t')}^{L} (\mu_1 - \mu_2) C_1(x, t')\, dx\, dt' \quad \text{for } t \in (0, t^*].$$

This shows that $R_1(t) > R_2(t)$ for all $t \in (0, t^*]$. Hence, by definition of t^*, we must have $C_1(x^*, t^*) = C_2(x^*, t^*)$ for some $x^* \in [R_1(t^*), L] \subset [R_2(t^*), L]$. Let X^* be the characteristic curve such that

$$(X^*)'(t) = u_2(t, X^*(t)), \quad X^*(t^*) = x^*.$$

Then, denoting again $\tilde{C} = C_1 - C_2$, then by definition of X^*, $\tilde{C}(X^*(t), t) < 0$ for $t \in (0, t^*)$ and $\tilde{C}(X^*(t^*), t^*) = 0$, so that $\frac{D\tilde{C}}{Dt}(t^*) \ge 0$. However,

$$\begin{aligned}
\frac{D\tilde{C}}{Dt}(t^*) &= \frac{\partial \tilde{C}}{\partial t} + u_2 \frac{\partial \tilde{C}}{\partial x}\Big|_{(x,t)=(x^*,t^*)} \\
&= \left[\frac{\partial C_1}{\partial t} + u_1 \frac{\partial C_1}{\partial x}\right]_{(x,t)=(x^*,t^*)} - \left[\frac{\partial C_2}{\partial t} + u_2 \frac{\partial C_2}{\partial x}\right]_{(x,t)=(x^*,t^*)} + (u_2 - u_1)\frac{\partial C_1}{\partial x}\Big|_{(x,t)=(x^*,t^*)} \\
&\le \left[g(C_1) - \mu_1 C_1 \left(1 - \frac{C_1}{\theta}\right)\right]_{(x,t)=(x^*,t^*)} - \left[g(C_2) - \mu_2 C_2 \left(1 - \frac{C_2}{\theta}\right)\right]_{(x,t)=(x^*,t^*)} \\
&= -\left[(\mu_1 - \mu_2) C_1 \left(1 - \frac{C_1}{\theta}\right)\right]_{(x,t)=(x^*,t^*)} < 0
\end{aligned}$$

where we used the fact that $(u_2 - u_1)\frac{\partial C_1}{\partial x} \le 0$ (due to (4.8) and Lemma 4.1) for the first inequality, and that $C_1(x^*, t^*) = C_2(x^*, t^*)$ for the next equality. This is a contradiction to $\frac{D\tilde{C}}{Dt}(t^*) \ge 0$. Hence $t^* \in I$ and I must be closed, i.e. (4.5) - (4.7) hold for $t \in (0, T]$. □

By approximation, we get the following comparison theorem.

Theorem 4.3. *If*

$$\mu_1 \ge \mu_2, \quad \frac{\partial \mu_1}{\partial x} \le 0, \quad \mu_2 \le \beta \quad \textit{for all } (x,t),\ 0 < t \le T,$$

then

$$R_1(t) \ge R_2(t), \quad C_1(x,t) \le C_2(x,t), \quad u_1 \ge u_2 \quad \textit{for all } R_1(t) \le x \le L,\ 0 \le t \le T.$$

5. Asymptotic behaviors

Given $\mu(x,t) \geq 0$, let $(C(x,t), u(x,t), R(t))$ be the corresponding solution to the free boundary problem (2.2), (2.6), (2.7) with the conditions (2.5), (2.8), (2.9), and set

$$B(x,t) = C_0 - C(x,t).$$

From (2.2) and (2.4), we get

$$\begin{aligned}\frac{\partial B}{\partial t} + \frac{\partial}{\partial x}(uB) &= -d_C B + \mu(C_0 - B) + C_0 \frac{\partial u}{\partial x} \\ &= -d_C B + \mu(C_0 - B) - \frac{C_0}{\theta}[\beta B + \mu(C_0 - B)],\end{aligned}$$

or

$$\frac{\partial B}{\partial t} + \frac{\partial}{\partial x}(uB) = \left(-d_C - \frac{C_0 \beta}{\theta}\right) B + \mu \left(1 - \frac{C_0}{\theta}\right)(C_0 - B). \tag{5.1}$$

We also have,

$$0 \leq B(x,0) \leq C_0, \tag{5.2}$$

and

$$\frac{dR}{dt}(t) = \frac{1}{\theta} \int_{R(t)}^{L} [\beta B + \mu(C_0 - B)]\, dx. \tag{5.3}$$

By Lemma 3.1,

$$0 \leq B(x,t) \leq B_* < C_0 \quad \text{for} \quad R(t) < x < L,\, t > 0, \tag{5.4}$$

where

$$B_* := C_0 - \min\left\{\inf_{R_{\text{in}} < x < L} C_{\text{in}}, C_*\right\} = \max\left\{\sup_{R_{\text{in}} < x < L} B(x,0), C_0 - C_*\right\} \in (0, C_0). \tag{5.5}$$

Next, we compute

$$\begin{aligned}\frac{d}{dt}\left[\int_{R(t)}^{L} B(x,t)\, dx\right] &= \int_{R(t)}^{L} \frac{\partial B}{\partial t}(x,t)\, dx - B(R(t),t)\frac{dR(t)}{dt} \\ &= \int_{R(t)}^{L} \frac{\partial B}{\partial t}(x,t)\, dx + [uB]_{x=R(t)}^{L} \\ &= \left(-d_C - \frac{C_0\beta}{\theta}\right) \int_{R(t)}^{L} B\, dx + \left(1 - \frac{C_0}{\theta}\right) \int_{R(t)}^{L} \mu(C_0 - B)\, dx,\end{aligned} \tag{5.6}$$

where the second equality follows from (2.7), and the third one follows by integrating (5.1) with respect to $x \in [R(t), L]$.

Next, we introduce the averages of B, μ and μB:

$$\overline{B}(t) := \frac{1}{L - R(t)} \int_{R(t)}^{L} B(x,t)\,dx, \quad \overline{\mu}(t) := \frac{1}{L - R(t)} \int_{R(t)}^{L} \mu(x,t)\,dx,$$

and

$$\overline{\mu B}(t) := \frac{1}{L - R(t)} \int_{R(t)}^{L} \mu(x,t)B(x,t)\,dx.$$

Then

$$-\frac{d}{dt}\left(\log(L - R(t))\right) = \frac{\frac{dR}{dt}}{L - R(t)} = \frac{\beta}{\theta}\overline{B} + \frac{C_0}{\theta}\overline{\mu} - \frac{1}{\theta}\overline{\mu B}, \tag{5.7}$$

and

$$\begin{aligned} \frac{d}{dt}\overline{B}(t) &= \frac{\frac{dR}{dt}}{(L - R(t))^2} \int_{R(t)}^{L} B\,dx + \frac{1}{L - R(t)} \left[\frac{d}{dt} \int_{R(t)}^{L} B(x,t)\,dx\right] \\ &= \frac{\frac{dR}{dt}}{L - R(t)}\overline{B} + \left(-d_C - \frac{C_0\beta}{\theta}\right)\overline{B} + \left(1 - \frac{C_0}{\theta}\right)C_0\overline{\mu} - \left(1 - \frac{C_0}{\theta}\right)\overline{\mu B}, \end{aligned}$$

where we used (5.6) in the second equality. Hence, using (5.7), we obtain

$$\frac{d}{dt}\overline{B}(t) = -d_C\overline{B} - \frac{\beta}{\theta}(C_0 - \overline{B})\overline{B} + C_0\left(1 - \frac{C_0}{\theta} + \frac{\overline{B}}{\theta}\right)\overline{\mu}(t) - \left[\frac{\overline{B}}{\theta} + \left(1 - \frac{C_0}{\theta}\right)\right]\overline{\mu B} \tag{5.8}$$

Lemma 5.1. *There exist constants $M_1 > m_1 > 0$ such that*

$$m_1 \int_{t-1}^{t} \overline{\mu}(s)\,ds \le \overline{B}(t) \le B_* e^{-d_C t} + M_1 \int_0^t e^{-d_C(t-s)}\overline{\mu}(s)\,ds \quad \textit{for} \ \ t \ge 1.$$

Proof. By (5.8),

$$\begin{cases} \frac{d}{dt}\overline{B}(t) \le -d_C\overline{B}(t) + C_0\left(1 - \frac{C_0}{\theta} + \frac{\overline{B}}{\theta}\right)\overline{\mu}(t) \quad \text{for} \ \ t \ge 0, \\ \overline{B}(0) \le B_*, \end{cases}$$

where $B_* \in (0, C_0)$ is given in (5.5). It follows that

$$\overline{B}(t) \le B_* e^{-d_C t} + C_0\left(1 - \frac{C_0}{\theta} + \frac{\overline{B}}{\theta}\right)\int_0^t e^{-d_C(t-s)}\overline{\mu}(s)\,ds.$$

Similarly, by (5.8) and $0 \le B(x,t) \le B_*$, we have

$$\frac{d}{dt}\overline{B}(t) \ge -d_C\overline{B} - \frac{\beta C_0}{\theta}\overline{B}(t) + (C_0 - B_*)\left(1 - \frac{C_0}{\theta}\right)\overline{\mu}(t)$$

which gives the estimate

$$\overline{B}(t) \ge (C_0 - B_*)\left(1 - \frac{C_0}{\theta}\right)\int_0^t e^{-(d_C+\beta C_0/\theta)(t-s)}\overline{\mu}(s)\,ds \ge m_1\int_{t-1}^t \overline{\mu}(s)\,ds.$$

□

Theorem 5.2. *The following dichotomy holds:*

(a) *If* $\displaystyle\int_0^\infty \overline{\mu}(s)\,ds = +\infty$, *then* $\displaystyle\lim_{t\to\infty} R(t) = L$.

(b) *If* $\displaystyle\int_0^\infty \overline{\mu}(s)\,ds < +\infty$, *then* $\displaystyle\lim_{t\to\infty} R(t) < L$.

Proof. We begin with the case that $\int_0^\infty \overline{\mu}(s)\,ds = +\infty$. Using the fact that $\overline{\mu B}(t) \le B_*\overline{\mu}(t)$ and (5.7), we have

$$-\frac{d}{dt}\left[\log(L - R(t))\right] \ge \frac{\beta}{\theta}\overline{B}(t) + \frac{C_0 - B_*}{\theta}\overline{\mu}(t) \ge \frac{C_0 - B_*}{\theta}\overline{\mu}(t).$$

This gives

$$\log\frac{L - R_{\text{in}}}{L - R(t)} \ge \frac{C_0 - B_*}{\theta}\int_0^t \overline{\mu}(s)\,ds \to \infty \qquad \text{as } \ t \to \infty,$$

i.e. $R(t) \nearrow L$ as $t \to \infty$. This proves (a).

For (b), assume that $\int_0^\infty \overline{\mu}(s)\,ds < +\infty$. By (5.7) again,

$$-\frac{d}{dt}\left[\log(L - R(t))\right] \le \frac{\beta}{\theta}\overline{B}(t) + \frac{C_0}{\theta}\overline{\mu}(t),$$

and using Lemma 5.1, we get

$$-\frac{d}{dt}\left[\log(L - R(t))\right] \le M\left(B_*e^{-d_C t} + \int_0^t e^{-d_C(t-s)}\overline{\mu}(s)\,ds + \overline{\mu}(t)\right),$$

for some constant M. Hence, by integration,

$$\begin{aligned}
\log \frac{L - R_{\rm in}}{L - R(\infty)} &\le M \left(\frac{B_*}{d_C} + \int_0^\infty \int_0^t e^{-d_C(t-s)} \overline{\mu}(s)\, ds dt \int_0^\infty \overline{\mu}(t)\, dt \right) \\
&= M \left(\frac{B_*}{d_C} + \int_0^\infty \int_s^\infty e^{-d_C(t-s)} \overline{\mu}(s)\, dt ds + \int_0^\infty \overline{\mu}(s)\, ds \right) \\
&= M \left(\frac{B_*}{d_C} + \int_0^\infty e^{-d_C s}\, ds \int_0^\infty \overline{\mu}(s)\, ds + \int_0^\infty \overline{\mu}(s)\, ds \right) \\
&= M' \left(1 + \int_0^\infty \overline{\mu}(s)\, ds \right) < +\infty,
\end{aligned}$$

so that $R(\infty) < L$. This proves (b). □

Corollary 5.3. *If $\mu(x,t) = k(t)(L-x)^\alpha$ for some constant $\alpha \ge 0$, then $R(\infty) = L$ if and only if $\int_0^\infty k(t)\, dt = +\infty$.*

Proof. In what follows, we denote by m_i several different positive constants. We begin by expressing $\bar{\mu}(t)$ in terms of $k(t)$:

$$\overline{\mu}(t) = \frac{1}{L - R(t)} \int_{R(t)}^L k(t)(L-x)^\alpha\, dx = \frac{k(t)}{\alpha+1}(L - R(t))^\alpha. \tag{5.9}$$

Suppose $\int_0^\infty k(t)\, dt = +\infty$. From the proof of Theorem 5.2(a), we have

$$-\frac{\frac{d}{dt}(L - R(t))}{L - R(t)} \ge m_2 \overline{\mu}(t).$$

Using (5.9), we get

$$-\frac{d}{dt}(L - R(t)) \ge m_3 k(t)(L - R(t))^{1+\alpha}$$

which we can integrate to get

$$\frac{1}{(L - R(t))^\alpha} - \frac{1}{(L - R_{\rm in})^\alpha} \ge m_4 \int_0^t k(s)\, ds.$$

This proves that $R(\infty) = L$ if $\int_0^\infty k(s)\, ds = +\infty$.

On the other hand, if $\int_0^\infty k(s)\, ds < +\infty$, then from (5.9), $\int_0^\infty \overline{\mu}(s)\, ds < +\infty$, and hence $R(\infty) < +\infty$, by Theorem 5.2(b). □

Corollary 5.4. *If for some $t_0 > 0$ and $\epsilon > 0$,*

$$\mu(x,t) = 0 \quad \text{for } \; L - \epsilon < x < L,\; t > t_0, \tag{5.10}$$

then $R(\infty) < L$.

Proof. Suppose not, then there exists a $t_1 > t_0$ such that $R(t) > L - \epsilon$ for all $t \geq t_1$, but then $\overline{\mu}(t) = 0$ for all $t \geq t_1$, and $R(\infty) < L$ by Theorem 5.2(b). $\square$

In case $\mu \equiv 0$, we can get a more precise value for $L - R(\infty)$ by considering the dynamics of C. First, we claim the following identity.

$$\int_{R(T)}^{L} C(x,T)\,dx = \int_{R(t_0)}^{L} C(x,t_0)\,dx + \int_{t_0}^{T}\left[\int_{R(t)}^{L} d_C(C_0 - C(x,t))\,dx\right]dt. \tag{5.11}$$

Indeed, fix $t \in [t_0, T]$ and integrate (2.2) over $x \in [R(t), L]$, we get

$$\begin{aligned}
\frac{d}{dt}\int_{R(t)}^{L} C\,dx &= \int_{R(t)}^{L} \frac{\partial C}{\partial t}\,dx - C(R(t),t)R'(t) \\
&= \int_{R(t)}^{L} \frac{\partial C}{\partial t}\,dx - \big[u(x,t)C(x,t)\big]_{x=R(t)}^{L} \\
&= \int_{R(t)}^{L} \left[\frac{\partial C}{\partial t} + \frac{\partial}{\partial x}(uC)\right]\,dx \\
&= \int_{R(t)}^{L} \left[A_C - d_C C\right]\,dx = \int_{R(t)}^{L} d_C(C_0 - C)\,dx
\end{aligned}$$

where we used $u(R(t),t) = \frac{d}{dt}R(t)$ and $u(L,t) = 0$ for the second equality, and $A_C = d_C C_0$ for the last equality. Integrating the result over $t \in [t_0, T]$, we obtain (5.11).

Next, we consider $C(x,t)$ along characteristics, for $t > t_0$,

$$\frac{DC}{Dt} \equiv \frac{\partial C}{\partial t} + u\frac{\partial C}{\partial x} = A_C - d_C C - C\frac{\partial u}{\partial x} = d_C(C_0 - C) + \frac{\beta}{\theta}(C_0 - C)C$$

i.e.

$$\frac{DC}{Dt} = (C_0 - C)\left(d_C + \frac{\beta}{\theta}C\right). \tag{5.12}$$

We see that C is uniformly increasing to C_0 along characteristics, so that $C(x,t) \to C_0$ as $t \to \infty$ uniformly in x. Taking $T \to \infty$ in (5.11) we get,

$$(L - R(\infty))C_0 = \int_{R(t_0)}^{L} C(x,t_0)\,dx + \int_{t_0}^{\infty}\left[\int_{R(t)}^{L} d_C(C_0 - C(x,t))\,dx\right]dt. \tag{5.13}$$

6. A two-phase mathematical model

The mathematical model of RA in [27] is a two-phase model. One phase is the region occupied by the synovial membrane, Ω_0, defined by

$$\Omega_0 = \{(x,t) : 0 \leq x \leq R(t),\ t > 0\},$$

and another phase is the cartilage region, Ω, defined by

$$\Omega = \{(x,t) : R(t) \leq x \leq L,\ t > 0\}.$$

The interface

$$\Gamma = \{(R(t),t) :\ t > 0\}$$

is a free boundary. In Ω we have the same equations as in the one-phase model, with the inflammation μ given by

$$\mu(x,t) = d_{CT_\alpha} \frac{T_\alpha(x,t)}{K_\alpha + T_\alpha(x,t)} \tag{6.1}$$

where $T_\alpha = T_\alpha(x,t)$ is the inflammatory cytokine TNF-α (tumor necrosis factor alpha), and K_α is the half-saturation constant. The inflammation develops in Ω_0 and spreads into Ω. In Ω_0 there is a system of PDEs consisting of three equations for three different types of cells, and of a large number of cytokines which the cells secrete [27]. We shall consider here a simplified model consisting of just one cytokine, namely T_α, and one type of cells, fibroblasts (F), which are activated by T_α and also secrete T_α. The two-phase model's equations are given as follows:

Within the synovial membrane region Ω_0,

$$\frac{\partial F}{\partial t} - \delta_F \frac{\partial^2 F}{\partial x^2} = \lambda_F F \left(1 - \frac{F}{F_0}\right) + \lambda_{FT_\alpha} \frac{T_\alpha}{K_\alpha + T_\alpha} F - d_F F, \tag{6.2}$$

$$\frac{\partial T_\alpha}{\partial t} - \delta_{T_\alpha} \frac{\partial^2 T_\alpha}{\partial x^2} = \lambda_{T_\alpha F} F - d_{T_\alpha} T_\alpha - d_{T_\alpha A} T_\alpha A. \tag{6.3}$$

Within the cartilage region Ω,

$$\frac{\partial C}{\partial t} + \frac{\partial}{\partial x}(uC) = A_C - d_C C - d_{CT_\alpha} \frac{T_\alpha}{K_\alpha + T_\alpha} C, \tag{6.4}$$

$$\frac{\partial T_\alpha}{\partial t} - \delta_{T_\alpha} \frac{\partial^2 T_\alpha}{\partial x^2} = -d_{T_\alpha} T_\alpha - d_{T_\alpha C} \frac{T_\alpha}{K_\alpha + T_\alpha} C, \tag{6.5}$$

where, as in equations (2.4)-(2.7),

$$-\frac{\partial u}{\partial x}=\frac{1}{\theta}\left[\beta(C_0-C)+d_{CT_\alpha}\frac{T_\alpha}{K_\alpha+T_\alpha}C\right], \quad u(L,t)=0, \tag{6.6}$$

for $R(t)\le x\le L$ and $t>0$, and

$$\frac{dR(t)}{dt}=\frac{1}{\theta}\int_{R(t)}^{L}\left[\beta(C_0-C)+d_{CT_\alpha}\frac{T_\alpha}{K_\alpha+T_\alpha}C\right]dx\,. \tag{6.7}$$

Here, the second term on the right-hand side of (6.2) represents the activation of F by T_α, the last term in the right-hand side of (6.3) is the depletion of T_α by anti-TNF-α drug A (e.g. infliximab), and the last term on the right-hand side of (6.4) represents the death of chondocytes C caused by TNF-α. All the parameters in the above equations are positive. We also note that, in [27], $d_{CT_\alpha}<\beta$, so that the inflammation $\mu(x,t)$ given by (6.1) satisfies the condition (4.4).

We next impose boundary conditions on F and T_α. We take

$$\left.\frac{\partial F}{\partial x}\right|_{x=0}=-\nu_F, \quad \text{and} \quad F|_{x=R(t)}=0, \tag{6.8}$$

where $-\nu_F>0$ is the rate of the influx of F into the membrane region from the peripheral blood,

$$\left.\frac{\partial T_\alpha}{\partial x}\right|_{x=0}=\left.\frac{\partial T_\alpha}{\partial x}\right|_{x=L}=0, \tag{6.9}$$

and also assume that

$$T_\alpha \ \text{and}\ \frac{\partial T_\alpha}{\partial x} \ \text{are continuous across the free-boundary}\ \Gamma. \tag{6.10}$$

We next prescribe initial conditions:

$$\begin{cases} F(x,0)=F_{\text{in}}(x)\ge 0 & \text{for } 0\le x\le R_{\text{in}},\\ C(x,0)=C_{\text{in}}(x), \ \text{and}\ 0\le C_{\text{in}}(x)\le C_0 & \text{for } R_{\text{in}}\le x\le L,\\ T_\alpha(x,0)=T_{\alpha,\text{in}}(x)\ge 0 & \text{for } 0\le x\le L, \end{cases} \tag{6.11}$$

where

$$F_{\text{in}}\in C^{2+\gamma}([0,R_{\text{in}}]), \quad C_{\text{in}}\in C^{2+\gamma}([R_{\text{in}},L]), \quad \text{and} \quad T_{\alpha,\text{in}}\in C^{2+\gamma}([0,L]) \tag{6.12}$$

for some $0<\gamma<1$, and $F_{\text{in}}, T_{\alpha,\text{in}}$ are positive, and satisfy the boundary conditions (6.8) and (6.9) respectively.

7. Existence and uniqueness of the two-phase problem

Theorem 7.1. *The system* (6.2)-(6.12) *has a unique solution such that* $F \in W^{2,1,p}_{x,t}(\Omega_0)$, $T_\alpha \in W^{2,1,p}_{x,t}(\Omega_0 \cup \Omega)$, $C \in C^1(\bar{\Omega})$, $u \in C^1(\bar{\Omega})$, $R(t) \in C^1([0,\infty);[0,L])$. *Furthermore,* $F \geq 0, T_\alpha \geq 0, C \geq 0$ *in their respective domains, and* $u(x,t) > 0$ *in* Ω.

Proof. We will proceed with a contraction mapping argument. Let $T > 0$, $K_0 > 0$ and set

$$Y_T := \Big\{ T_\alpha \in \mathbb{X} \,\Big|\, T_\alpha(x,0) = T_{\alpha,in}(x) \text{ for all } x \in [0,L],\ \|T_\alpha\|_{\mathbb{X}} \leq K_0 \Big\},$$

where $\mathbb{X} = C([0,L] \times [0,T])$.

Step 1. Given $T_\alpha^{(1)} \in Y_T$, define

$$\mu^{(1)}(x,t) := -d_{CT_\alpha} \frac{T_\alpha^{(1)}}{K_\alpha + T_\alpha^{(1)}}.$$

By Theorem 3.3, there exist functions

$$R^{(1)} \in C^1([0,T]), \quad (C^{(1)}, u^{(1)}) \in C^1(\bar{\Omega}^{(1)}; \mathbb{R}^2),$$

where $\Omega^{(1)} = \{(x,t) :\ 0 < t < T,\ R^{(1)}(t) \leq x \leq L\}$, such that (6.4), (6.6) and (6.7) are satisfied by $(R^{(1)}, C^{(1)}, u^{(1)}, T_\alpha^{(1)})$.

Step 2. Given $(T_\alpha^{(1)}, R^{(1)})$, let $F^{(1)} \in W^{2,1,p}([0,L] \times [0,T] \setminus \Omega^{(1)})$ be the unique solution to

$$\frac{\partial F^{(1)}}{\partial t} - \delta_F \frac{\partial^2 F^{(1)}}{\partial x^2} = \lambda_F F^{(1)} \left(1 - \frac{F^{(1)}}{F_0}\right) + \lambda_{FT_\alpha} \frac{T_\alpha^{(1)}}{K_\alpha + T_\alpha^{(1)}} F^{(1)} - d_F F^{(1)}, \tag{7.1}$$

for $0 \leq x \leq R^{(1)}(t)$, $0 \leq t \leq T$, with the initial boundary conditions (6.8) and (6.12).

Step 3. Given $(T_\alpha^{(1)}, R^{(1)}, C^{(1)}, F^{(1)})$ as above. Let $T_\alpha^{(2)} \in W^{2,1,p}((0,L) \times (0,T))$ be the unique solution to the following linear parabolic equation:

$$\begin{cases} \frac{\partial T_\alpha^{(2)}}{\partial t} - \delta_{T_\alpha} \frac{\partial^2 T_\alpha^{(2)}}{\partial x^2} = \lambda_{T_\alpha F} F^{(1)} - d_{T_\alpha} T_\alpha^{(1)} - d_{T_\alpha A} T_\alpha^{(1)} A, & \text{in } ([0,L] \times [0,T]) \setminus \Omega^{(1)}, \\ \frac{\partial T_\alpha^{(2)}}{\partial t} - \delta_{T_\alpha} \frac{\partial^2 T_\alpha^{(2)}}{\partial x^2} = -d_{T_\alpha} T_\alpha^{(1)} - d_{T_\alpha C} \frac{T_\alpha^{(1)}}{K_\alpha + T_\alpha^{(1)}} C^{(1)}, & \text{in } ([0,L] \times [0,T]) \cap \Omega^{(1)}, \end{cases} \tag{7.2}$$

with boundary conditions (6.9) - (6.12).

Step 4. Define the mapping $\Psi : Y_T \to Y_T$ by $\Psi(T_\alpha^{(1)}) = T_\alpha^{(2)}$. We claim that Ψ is a contraction mapping, provided T is sufficiently small.

To this end, let $T_\alpha^{(1a)}, T_\alpha^{(1b)} \in Y_T$ be given, and let $(R^{(1a)}, C^{(1a)}, u^{(1a)}, \mu^{(1a)}, F^{(1a)}, T_\alpha^{(2a)})$ and $(R^{(1b)}, C^{(1b)}, u^{(1b)}, \mu^{(1b)}, F^{(1b)}, T_\alpha^{(2b)})$ be given by Steps 1, 2 and 3. Now, for each symbol $G \in \{R, C, u, \mu, F, T\}$ and $i = 1, 2$, define $\tilde{G}^{(i)} = G^{(ia)} - G^{(ib)}$. First, we estimate $\tilde{F}^{(1)} = F^{(1a)} - F^{(1b)}$. Let $R_*^{(1)}(t) = \min\{R^{(1a)}(t), R^{(1b)}(t)\}$. By parabolic L^p estimates, we deduce that $F^{(1a)}$ (resp. $F^{(1b)}$) is uniformly bounded in $W^{2,1,p}([0,L]\times[0,T]\setminus\Omega^{(1a)})$ (resp. $W^{2,1,p}([0,L]\times[0,T]\setminus\Omega^{(1b)})$). In particular they are uniformly Lipschitz in x. Since they also vanish on the free boundary (by (6.8)), we get

(7.3)
$$\sup_{R_*^{(1)}(t)\le x\le R^{(1a)}(t)}|F^{(1a)}(R_*^{(1)}(t),t)|+\sup_{R_*^{(1)}(t)\le x\le R^{(1b)}(t)}|F^{(1b)}(R_*^{(1)}(t),t)|\le M_0|R^{(1a)}(t)-R^{(1b)}(t)|;$$

hereafter M_0 denotes a generic constant that does not depend on $0<T<1$. Hence we may estimate $\tilde{F}^{(1)}$ in the smaller domain

$$\Omega_*^{(1)}:=\{(x,t):0\le x\le R_*^{(1)}(t),\ t\in[0,T]\}$$

to get

$$\|\tilde{F}^{(1)}\|_{C(\Omega_*^{(1)})}\le M_0\left[\sup_{[0,T]}|\tilde{F}^{(1)}(R_*^{(1)}(t),t)|+\|\tilde{T}_\alpha^{(1)}\|_{C([0,L]\times[0,T])}\right]. \tag{7.4}$$

If we extend $F^{(1a)}, F^{(1b)}$ trivially to all of $[0,L]\times[0,T]$, then we may combine (7.3) and (7.4) to obtain

$$\|\tilde{F}^{(1)}\|_{C([0,L]\times[0,T])}\le M_0\left[\sup_{[0,T]}|\tilde{R}^{(1)}(t)|+\|\tilde{T}_\alpha^{(1)}\|_{C([0,L]\times[0,T])}\right] \tag{7.5}$$

Next, we recall the global estimate for strong solutions of parabolic Neumann problems [30, Theorem 7.35, p.185]: Suppose $u\in W^{1,2}((0,L)\times(0,1))$ and satisfies $u(x,0)\equiv 0$ for $x\in[0,L]$ and $u_x(0,t)=u_x(L,t)=0$ for $t\in(0,1)$, then

$$\|u_t\|_{L^2((0,L)\times(0,1))}+\|u_{xx}\|_{L^2((0,L)\times(0,1))}\le M_0\|u_t-u_{xx}\|_{L^2((0,L)\times(0,1))}.$$

In particular, for each $0<T<1$,

$$\|u\|_{C([0,L]\times[0,T])}\le M_0T^{1/2}\|u_t\|_{L^2((0,L)\times(0,1))}\le M_0T^{1/2}\|u_t-u_{xx}\|_{L^2((0,L)\times(0,1))}.$$

Applying the above estimate to (7.2), it is not difficult to see that

$$\begin{aligned}\sup_{[0,T]}\left\|\tilde{T}_\alpha^{(2)}\right\|_{C([0,L]\times[0,T])} &\le M_0T^{1/2}\Big[\sup_{[0,T]}|\tilde{R}^{(1)}|+\left\|\tilde{T}_\alpha^{(1)}\right\|_{C([0,L]\times[0,T])}\\ &\qquad+\|\tilde{F}^{(1)}\|_{C([0,L]\times[0,T])}+\left\|\hat{C}^{(1a)}-\hat{C}^{(1b)}\right\|_{C([R_{\rm in},L]\times[0,T])}\Big]\end{aligned}$$

where $\hat{C}^{(1a)}(x,t)=C^{(1a)}(X^{(1a)}(x,t),t)$ and $\hat{C}^{(1b)}(x,t)=C^{(1b)}(X^{(1b)}(x,t),t)$. Next, we use (7.5), Remark 3.4 and the relation $\mu=d_{CT_\alpha}\frac{T_\alpha}{K_\alpha+T_\alpha}$ to deduce that

$$\left\|\tilde{T}_\alpha^{(2)}\right\|_{C([0,L]\times[0,T])}\le M_0T^{1/2}\left\|\tilde{T}_\alpha^{(1)}\right\|_{C([0,L]\times[0,T])}.$$

where M_0 depends on the constant C_0 and does not depend on T so long as $T \le 1$. Hence, we may choose T small enough so that $M_0 T^{1/2} \le 1/2$, so that we have

$$\left\| \Psi(T_\alpha^{(1a)}) - \Psi(T_\alpha^{(1b)}) \right\|_{C([0,L]\times[0,T])} \le \frac{1}{2} \left\| T_\alpha^{(1a)} - T_\alpha^{(1b)} \right\|_{C([0,L]\times[0,T])}$$

i.e. Ψ defines a contraction in Y_T. The above proof can be modified to show that Ψ maps Y_T into itself if K_0 is sufficiently large. Hence, for such a T, Ψ has a unique fixed point $T_\alpha^* \in Y_T$, which, together with the corresponding (R^*, C^*, u^*, F^*) (obtained by Steps 1 and 2), defines the unique solution to the system (6.2)-(6.12) in a short time interval $[0, T]$.

Finally, we claim that solutions exists globally in $t \ge 0$. By standard maximum principle applying to (6.2) - (6.5) that the following estimates holds uniformly:

$$0 \le C(x,t) \le C_0, \quad 0 \le F(x,t) \le \|F_{\text{in}}\|_{C([0,L])} e^{(\lambda_F + \lambda_{FT_\alpha} - d_F)t}$$

and that

$$0 \le T_\alpha(x,t) \le \|T_{\alpha,in}\|_{C([0,L])} + t\lambda_{T_\alpha F} \|F\|_{C([0,L]\times[0,T])},$$

which does not blow up in finite time. Hence the existence and unqiueness of solution (T_α, F, C, u, R) can be extended step by step to all $t \ge 0$. □

8. Monotonicity

Theorem 8.1. *If*

$$\frac{\partial F_{\text{in}}}{\partial x} \le 0, \quad \frac{\partial C_{\text{in}}}{\partial x} \ge 0, \quad \frac{\partial T_{\alpha,\text{in}}}{\partial x} \le 0, \tag{8.1}$$

then the solution $(F,\ C,\ T_\alpha)$ *satisfies:*

$$\frac{\partial F}{\partial x} \le 0 \quad \text{in } \Omega_0, \quad \frac{\partial C}{\partial x} \ge 0 \quad \text{in } \Omega, \quad \frac{\partial T_\alpha}{\partial x} \le 0 \quad \text{in } \Omega_0 \cup \Omega. \tag{8.2}$$

Proof. By the boundary condition (6.8), and by applying Hopf's boundary lemma at $x = R(t)$, we have

$$F_x(x,t) < 0 \quad \text{ for } x \in \{0,\ R(t)\}, \ \text{ and } t > 0. \tag{8.3}$$

Next, if we differentiate the equations (6.2)-(6.5) with respect to x, we get, formally,

$$\begin{aligned} &\frac{\partial F_x}{\partial t} - \delta_F \frac{\partial^2 F_x}{\partial x^2} \\ &= \lambda_F F_x \left(1 - \frac{2F}{F_0}\right) + \lambda_{FT_\alpha} \frac{T_\alpha}{K_\alpha + T_\alpha} F_x + \lambda_{FT_\alpha} \frac{K_\alpha}{(K_\alpha + T_\alpha)^2} (T_\alpha)_x F - d_F F_x \end{aligned} \tag{8.4}$$

in Ω_0,

$$\begin{aligned}
&\frac{\partial}{\partial t}(T_\alpha)_x - \delta_{T_\alpha}\frac{\partial^2}{\partial x^2}(T_\alpha)_x \\
&= \begin{cases} \lambda_{T_\alpha F}F_x - d_{T_\alpha}(T_\alpha)_x - d_{T_\alpha A}(T_\alpha)_x A & \text{in } \Omega_0 \\ -d_\alpha(T_\alpha)_x + d_{T_\alpha}(-C)\frac{K_\alpha}{(K_\alpha+T_\alpha)^2}(T_\alpha)_x + d_{CT_\alpha}(-C_x)\frac{T_\alpha}{K_\alpha+T_\alpha} & \text{in } \Omega. \end{cases}
\end{aligned} \tag{8.5}$$

and, as in (4.1),

$$\begin{aligned}
&\frac{\partial}{\partial t}(-C_x) + u\frac{\partial}{\partial x}(-C_x) \\
&= \left[-g'(C) + \frac{d_{CT_\alpha}T_\alpha}{K_\alpha+T_\alpha}\left(1-\frac{2C}{\theta}\right) + \frac{\partial u}{\partial x}\right](-C_x) + C\left(1-\frac{C}{\theta}\right)\frac{K_\alpha}{(K_\alpha+T_\alpha)^2}(T_\alpha)_x
\end{aligned} \tag{8.6}$$

in $\Omega_0 \cup \Omega$.

With the triplet (F, T_α, C) and u given, one can regard the x-derivative $(F_x, (T_\alpha)_x, -C_x)$ as a solution to the linear system (8.1)-(8.6) with the corresponding boundary condition (6.8) for F_x, $(T_\alpha)_x(x,t) = 0$ for $x = 0, L$ and $t > 0$, and initial conditions in the respective domains $(\Omega_0, \Omega_0 \cup \Omega, \Omega)$.

For any small $\epsilon > 0$, consider the system for $(F_x, (T_\alpha)_x, -C_x)$ where we add $-\epsilon$ to the right-hand side of the differential equations, $-\epsilon$ to the initial conditions, and $\pm\epsilon$ to the right-hand side of the boundary conditions, so the ϵ-solution

$$(F_x^\epsilon, (T_\alpha^\epsilon)_x, -C_x^\epsilon)$$

satisfies, for small t_0, the inequalities

$$\begin{cases} F_x^\epsilon < 0 & \text{in } \Omega \cap \{t < t_0\}, \\ (T_\alpha^\epsilon)_x < 0 & \text{in } (\Omega_0 \cup \Omega) \cap \{t < t_0\}, \\ -C_x^\epsilon < 0 & \text{in } \Omega \cap \{t < t_0\}. \end{cases} \tag{8.7}$$

We note that the solution $(F_x^\epsilon, (T_\alpha^\epsilon)_x, -C_x^\epsilon)$ exists. Furthermore, it converges to the solution $(F_x, (T_\alpha)_x, -C_x)$ as $\epsilon \to 0$. Hence if we can show that (8.7) holds for all $t_0 > 0$ then the assertion (8.2) follows.

To prove (8.7) for all $t_0 > 0$, we suppose to the contrary that there is some $t_0 > 0$ so that (8.7) holds for all $t < t_0$ but fails to hold at $t = t_0$. This means that one of the functions $F_x^\epsilon, (T_\alpha^\epsilon)_x, -C_x^\epsilon$ vanishes at some point (x_0, t_0).

Consider the case that $F_x^\epsilon(x_0, t_0) = 0$. By the ϵ-modified boundary conditions, (x_0, t_0) must be an interior point of Ω_0, and hence the left-hand side of the parabolic equation is non-negative at (x_0, t_0). Since $(T_\alpha^\epsilon)_x \le 0$ at (x_0, t_0), the right-hand side of the equation for F_x^ϵ is less than or equal to $-\epsilon$, which is a contradiction.

Finally, in the cases where $(T_\alpha^\epsilon)_x(x_0, t_0) = 0$ and $-C_x^\epsilon(x_0, t_0) = 0$ we can similarly derive a contradiction. $\square$

9. Drug slows cartilage destruction

We denote by $(F^A, C^A, T_\alpha^A, R^A)$ the solution of the system (6.2)-(6.12) and (8.1) for a dose A of the drug, and by (F, C, T_α, R) the solution of the system (6.2)-(6.12) and (8.1) with zero dose. We shall prove that the drug slows the destruction of the cartilage, that is,

$$R^A(t) < R(t) \quad \text{for all } t > 0. \tag{9.1}$$

But we will also show that

$$\lim_{t\to\infty} (L - R^A(t)) = 0, \tag{9.2}$$

that is, the drug cannot stop the eventual total destruction of the cartilage, as in the model of [27].

Theorem 9.1. *Assume the initial data satisfies* (8.1)*. If $A > 0$, then* (9.1) *holds.*

Proof. We first add $-\epsilon$ to the right-hand side of the equation for T_α^A, modify by $\pm\epsilon$ the boundary condition for T_α^A to ensure that $T_\alpha^A - T_\alpha$ cannot take maximum 0 at the boundary, and modify by ϵ the initial data $T_{\alpha,\text{in}}$ for T_α^A to ensure that

$$R^A(t) < R(t) \quad \text{for } 0 < t < t_0, \tag{9.3}$$

and

$$T_\alpha^A(x,t) < T_\alpha(x,t) \quad \text{in } (\Omega_0 \cup \Omega) \cap \{0 < t < t_0\}, \tag{9.4}$$

for t_0 sufficiently small. We claim that (9.3) holds for all t_0. To prove it we assume that there is a t_0 such that (9.3) holds while

$$R^A(t_0) = R(t_0) \tag{9.5}$$

and derive a contradiction.

We first show that, for this t_0, the inequality (9.4) holds. Indeed, otherwise there is a point (x_1, t_1) such that $t_1 < t_0$,

$$T_\alpha^A(x_1,t_1) = T_\alpha(x_1,t_1) \quad \text{and} \quad T_\alpha^A(x,t) < T_\alpha(x,t) \quad \text{in } (\Omega_0 \cup \Omega) \cap \{0 < t < t_1\}. \tag{9.6}$$

Applying Theorem 4.2, we deduce that

$$C^A(x,t) > C(x,t) \quad \text{for } R(t) \le x \le L,\ t < t_1. \tag{9.7}$$

Since $F > 0$ on $x = R^A(t)$, we deduce from (6.2), again by comparison, that

$$F^A(x,t) < F(x,t) \quad \text{for } 0 \le x \le R^A(t),\ t < t_1.$$

Next, we claim that $\tilde{T}_\alpha : T_\alpha - T_\alpha^A$ satisfies the following differential inequality:

$$\frac{\partial \tilde{T}_\alpha}{\partial t} - \delta_{T_\alpha} \frac{\partial^2 \tilde{T}_\alpha}{\partial x} + d_{T_\alpha} \tilde{T}_\alpha \geq \begin{cases} 0 & \text{for } 0 \leq x < R(t), x \neq R^A(t), \\ -d_{T_\alpha C} \frac{CK_\alpha}{(K_\alpha + T_\alpha^A)(K_\alpha + T_\alpha)} \tilde{T}_\alpha & \text{for } R(t) < x \leq L. \end{cases} \tag{9.8}$$

We divide the proof of (9.8) into three cases. First, for $0 \leq x < R^A(t)$, we have

$$\frac{\partial \tilde{T}_\alpha}{\partial t} - \delta_{T_\alpha} \frac{\partial^2 \tilde{T}_\alpha}{\partial x} + d_{T_\alpha} \tilde{T}_\alpha \geq \lambda_{T_\alpha F}(F - F^A) + d_{T_\alpha} T_\alpha^A A \geq 0.$$

Next, for $R^A(t) < x < R(t)$, we have

$$\frac{\partial \tilde{T}_\alpha}{\partial t} - \delta_{T_\alpha} \frac{\partial^2 \tilde{T}_\alpha}{\partial x} + d_{T_\alpha} \tilde{T}_\alpha = d_{T_\alpha C} \frac{T_\alpha^A C^A}{K_\alpha + T_\alpha^A} + \lambda_{T_\alpha F} F \geq 0. \tag{9.9}$$

Finally, for $R(t) < x < L$, we use $C_A \geq C$ to deduce

$$\begin{aligned} \frac{\partial \tilde{T}_\alpha}{\partial t} - \delta_{T_\alpha} \frac{\partial^2 \tilde{T}_\alpha}{\partial x} + d_{T_\alpha} \tilde{T}_\alpha &= d_{T_\alpha C} \left(-\frac{T_\alpha C}{K_\alpha + T_\alpha} + \frac{T_\alpha^A C^A}{K_\alpha + T_\alpha^A} \right) \\ &\geq d_{T_\alpha C} \left(-\frac{T_\alpha}{K_\alpha + T_\alpha} + \frac{T_\alpha^A}{K_\alpha + T_\alpha^A} \right) C \\ &= -d_{T_\alpha C} \frac{CK_\alpha}{(K_\alpha + T_\alpha^A)(K_\alpha + T_\alpha)} \tilde{T}_\alpha. \end{aligned}$$

This concludes the proof of (9.8). By applying the weak Harnack inequality [30, Theorem 7.37] to $\tilde{T}_\alpha$, we must have $\tilde{T}_\alpha(x, t_1) < 0$ for all $x \in [0, L]$. This contradicts the existence of (x_1, t_1). Hence, (9.4) holds as long as $R_A(t) < R(t)$ in $[0, t_0)$.

Having proved that (9.4) holds, we can now consider the two free boundary problems for (C^A, T_α^A, R^A) and (C, T_α, R). Recalling the monotonicity result of Theorem 8.1. we can then apply Theorem 4.2 to derive a contradiction to (9.5). We have thus proved that $R^A(t) < R(t)$ for all $t > 0$, in the case where we modified the original system by ϵ. Taking $\epsilon \to 0$, the proof of Theorem 9.1 is complete. □

Remark 9.2. *Theorem 9.1 extends to the case of two drugs, A and B, with B small and $A > B$. The only difference in the proof occurs in equation (9.9) in the region $\{(x, t) : R^A(t) < x < R(t)\}$. Setting $\tilde{T}_\alpha = T_\alpha^B - T_\alpha^A$, the modified equation is*

$$\frac{\partial \tilde{T}_\alpha}{\partial t} - \delta_{T_\alpha} \frac{\partial^2 \tilde{T}_\alpha}{\partial x^2} + d_{T_\alpha} \tilde{T}_\alpha = d_{T_\alpha C} \frac{T_\alpha^A C^A}{K_\alpha + T_\alpha^A} + \lambda_{T_\alpha F} F - d_{T_\alpha B} T_\alpha B \geq 0 \tag{9.10}$$

provided B is sufficiently small.

Remark 9.3. *Alternatively, one may formally differentiate the system of equations* (6.2) - (6.7) *in A, to yield a linearized problem in $\Omega_0 \cup \Omega$, where $\frac{dR}{dA}(t)$ has a separate equation in terms of $\frac{dF}{dA}, \frac{dT_\alpha}{dA}, \frac{dC}{dA}$. Upon deriving appropriate boundary conditions, one can observe that the smallness of the dosage (i.e. the right hand side of* (9.10) *is non-negative) is indeed crucial to preserve the monotonicity of the efficacy of the drug in terms of the dosage of drug. We also remark that for large dosage A, we expect that the efficacy varies very slowly with A and that the monotonicity may break down.*

Next, we prove that, no matter how large the amount of drug A, the cartilage will be eventually destroyed.

Theorem 9.4. *For any $A > 0$, $\lim_{t\to\infty} R^A(t) = L$.*

Proof. Let $(F^A, T^A_\alpha, C^A, R^A)$ be solution to (6.2)-(6.12) and (8.1), and define

$$\mu^A(x,t) := d_{T_\alpha C} \frac{T^A_\alpha(x,t)}{K_\alpha + T^A_\alpha(x,t)}$$

By Theorem 8.1,

$$\frac{\partial}{\partial x}\mu^A(x,t) \le 0$$

and hence we can use the comparison result (Theorem 4.2) and Corollary 5.3 to conclude that $R(\infty) = L$ if $\mu(x,t) \ge k(t)$ and $\int_0^\infty k(t)\,dt = \infty$. Thus, it is enough to show that $\liminf_{t\to\infty} \inf_{0<x<L} \mu^A(x,t) > 0$ or, equivalently,

$$\liminf_{t\to\infty} \inf_{0<x<L} T^A_\alpha(x,t) > 0. \tag{9.11}$$

To this end, we first claim that for some positive constants δ, η there holds:

$$\liminf_{t\to\infty} \int_0^\delta F^A(x',t)\,dx'\,ds \ge \eta. \tag{9.12}$$

Indeed, by parabolic L^p estimates and interpolation [29, p. 80, Lemma 3.3],

$$\left\| \frac{\partial F^A}{\partial x} \right\|_{C^\gamma([0,R_{\rm in}]\times[t,t+1])} \le \left\| F^A \right\|_{W^{2,1,p}([0,R_{\rm in}]\times[t,t+1])} \le C,$$

for some large $p > 1$ and $0 < \gamma < 1$. Recalling (6.8), we deduce that, for some small $\delta > 0$,

$$-\frac{\partial F^A}{\partial x}(x,t) \ge -\frac{\partial F^A}{\partial x}(0,t) - \frac{\nu_F}{2} = \frac{\nu_F}{2} > 0 \quad \text{for } 0 < x < 2\delta \text{ and } t \gg 1.$$

Since $F(x,t) \geq 0$, it follows that

$$\liminf_{t\to\infty} F(x,t) \geq \frac{\nu_F}{2}\delta \quad \text{for } 0 < x < \delta,$$

so that (9.12) holds with $\eta = \frac{\nu_F}{2}\delta^2$.

Next, we integrate (6.3) over $[0, R^A(t)] \times [t, t+1]$ and (6.5) over $[R^A(t), L] \times [t, t+1]$, and add the resulting equations to obtain:

$$\begin{aligned}
&\frac{d}{dt}\left[\int_t^{t+1}\int_0^L T_\alpha^A(x,s)\,dxds\right] \\
&\geq \lambda_{T_\alpha F}\int_t^{t+1}\int_0^{R^A(s)} F^A(x,s)\,dxds - (d_{T_\alpha} + d_{T_\alpha A}A)\int_t^{t+1}\int_0^{R^A(s)} T_\alpha^A(x,s)\,dxds \\
&\quad - \left(d_{T_\alpha} + \frac{d_{T_\alpha C}C_0}{K_\alpha}\right)\int_t^{t+1}\int_{R^A(s)}^L T_\alpha^A(x,t)\,dxds \\
&\geq \lambda_{T_\alpha F}\int_t^{t+1}\int_0^{\delta} F^A(x,s)\,dxds - M'\int_t^{t+1}\int_0^L T_\alpha^A(x,s)\,dxds,
\end{aligned}$$

where $M' = d_{T_\alpha} + d_{T_\alpha A}A + \frac{d_{T_\alpha C}C_0}{K_\alpha}$. Using Gronwall inequalities and (9.12), we get

$$\liminf_{t\to\infty}\int_t^{t+1}\int_0^L T_\alpha\,dxds \geq \frac{\lambda_{T_\alpha F}}{M'}\liminf_{t\to\infty}\int_t^{t+1}\int_0^\delta F^A(x,s)\,dxds \geq \frac{\lambda_{T_\alpha F}}{M'}\eta > 0,$$

and assertion (9.11) then follows by the weak Harnack's inequality [30, Theorem 7.37]. $\square$

10. Conclusion

The present paper considers a two-phase free boundary problem based on a model of rheumatoid arthritis. In one phase (the synovial fluid) pro-inflammatory cells (F) produce inflammatory cytokines (T_α), and the cytokine then diffuse into the second phase (the cartilage) where they increase the death rate of chondrocytes, which results in a gradual destruction of the cartilage. In the model's simplified geometry, the free boundary is a function $x = R(t)$ and the cartilage thickness is $L - R(t)$. We proved global existence and uniqueness of solutions, and several properties of the free boundary. The model includes also a drug A which degrades the inflammation. It was shown that even a small amount of drug A reduces the growth of the free boundary $x = R(t)$. On the other hand, no matter how large A is, the cartilage eventually is totally destroyed in the sense that the thickness of cartilage $L - R(t) \searrow 0$ as $t \to \infty$.

Future work would be to extend the results of this paper to a two-dimensional geometry with free boundary $y = R(x,t)$, the interface between the synovial fluid phase

$$\{(x,y,t) :\ -K \leq x \leq K,\ 0 \leq y \leq R(x,t)\}$$

and the cartilage phase

$$\{(x, y, t) : \ -K \leq x \leq K, \ R(x, t) \leq y \leq L\},$$

where $K \in (0, \infty)$ or $K = \infty$.

References

[1] C. Xue, A. Friedman and C. Sen, A mathematical model of ischemic cutaneous wounds, Proc. Natl. Acad. Sci. USA **106** (2009), pp.16782-16787.

[2] A. Friedman and C. Xue, A mathematical model for chronic wounds, Math. Biosci. Eng. **8** (2011), pp. 253-261.

[3] W. Hao and A. Friedman, The LDL-HDL profile determine the risk of atherosclerosis: A mathematical model, Plos One **9** (2014): e90497.

[4] A. Friedman and W. Hao, A mathematical model of atherosclerosis with reverse cholesterol transport and associated risk factors, Bull. Math. Biol. **77** (2015), pp. 758-781.

[5] W. Hao, S. Gong, S. Wu, J. Xu, M.R. Go, A. Friedman, and D. Zhu, A mathematical model of aortic aneurysm formation, PloS one **12** (2017): e0170807.

[6] W. Hao, L.S. Schlesinger and A. Friedman, Modeling granulomas in response to infection in the lung, PloS one **11** (2016): e0148738.

[7] N. Siewe, A.A. Yakubu, A.R. Satoskar, and A. Friedman, Granuloma formation in leishmaniasis: A mathematical model, J. Theor. Biol. **412** (2017), pp.48-60.

[8] I. Klapper and J. Dockery, Mathematical description of microbial biofilms, SIAM Rev. **52** (2009), pp. 359-371.

[9] Q. Wang and T. Zhang, Review of mathematical models for biofilms, Solid State Commun. **150** (2010), pp. 1009-1022.

[10] F.F. Weller, A free boundary problem modeling thrombus growth, J. Math. Biol. **61** (2010), pp. 805-818.

[11] A. Friedman and X. Lai, Combination therapy for cancer with oncolytic virus and checkpoint inhibitor: A mathematical model. PloS one **13(2)**, e0192449.

[12] X. Lai, A. Stiff, M. Duggan, R. Wesolowski, W. E. Carson and A. Friedman, Modeling combination therapy for breast cancer with BET and immune checkpoint inhibitors, Proc. Nat. Acad. Sci. **115** (2018), pp. 5534-5539.

[13] X. Lai and A. Friedman, Mathematical modeling in scheduling cancer treatment with combination of VEGF inhibitor and chemotherapy drugs, J. Theor. Biol. **462** (2019), pp. 290-298.

[14] A. Friedman, B. Hu and C. Xue. Analysis of a mathematical model of ischemic cutaneous wounds, SIAM J. Math. Anal. **42** (2010), pp.2013-2040.

[15] A. Friedman, B. Hu and C. Xue, A three dimensional model of wound healing: Analysis and computation, Discrete Contin. Dyn. Syst. B, **17** (2012), pp. 2691-2712.

[16] A. Friedman, B. Hu and C. Xue, A two phase free boundary problem for a system of Stokes equations with application to biofilm growth, Arch. Rat. Mech. Anal. **211** (2014), pp. 257-300.

[17] F.F. Weller, Platelet deposition in non-parallel flow. Influence of shear stress and changes in surface reactivity, J Math Biol **57** (2008), pp. 333-359.

[18] A. Friedman and K.-Y. Lam, On the stability of steady states in a granuloma model, J. Differential Equations **256** (2014), pp. 3743-3769.

[19] A. Friedman, C.-Y. Kao and R. Leander, Dynamics of radially symmetric granulomas, J. Math. Anal. Appl. **412** (2014), pp. 776-791.

[20] A. Friedman W. Hao and B. Hu, A free boundary problem for steady small plaques in the artery and their stability, J. Differential Equations **259** (2015), pp. 1227-1255.

[21] A. Friedman, Mathematical biology. Modeling and analysis. CBMS Regional Conference Series in Mathematics, 127. Published for the Conference Board of the Mathematical Sciences, Washington, DC; by the American Mathematical Society, Providence, RI, 2018. viii+100 pp.

[22] Y. Wang, and S. Guo, A SIS reaction-diffusion model with a free boundary condition and nonhomogeneous coefficients, Discrete Contin. Dyn. Syst. Ser. B **24** (2019), pp. 1627-1652.

[23] Y. Du and Z. Guo, Spreading-vanishing dichotomy in a diffusive logistic model with a free boundary II, J. Differential Equations **250** (2011), pp. 4336-4366.

[24] Y. Du, and Z. Lin, Spreading-vanishing dichotomy in the diffusive logistic model with a free boundary. SIAM J. Math. Anal. **42** (2010), pp. 377-405.

[25] M. Wang, The diffusive logistic equation with a free boundary and sign-changing coefficient, J. Differential Equations **258** (2015), pp. 1252-1266.

[26] H. Pan, R. Xing and B. Hu, A free boundary problem with two moving boundaries modeling grain hydration, Nonlinearity 31 (2018), no. 8, pp. 3591-3616.

[27] N. Moise and A. Friedman, Rheumatoid arthritis - a mathematical model, J. Theor. Biol., **461** (2019), pp. 17-33.

[28] X. Chen and A. Friedman, A free boundary problem for an elliptic-hyperbolic system: an application to tumor growth, SIAM J. Math. Anal. **35** (2003), no. 4, pp. 974-986.

[29] O.A. Ladyzenskaja, V.A. Solonnikov and N.N. Ural'ceva, Linear and Quasi-linear Equations of Parabolic Type, AMS Trans. 23, Providence, RI, 1968.

[30] G.M. Lieberman, Second Order Parabolic Differential Equations. World Scientific, 1996.